

**REMARKS**

Applicants have made the above amendments as a partial response to the Notice to Comply (Paper No. 7), mailed December 10, 2001. Applicants are also enclosing with this communication a substitute paper copy of the sequence listing and a substitute CRF under separate cover.

Applicants have made many of the changes required by the Examiner. Specifically:

- a) The amino acid sequence DDDDK disclosed on pages 9, line 25 and page 30, line 15 has been added as SEQ ID NO: 15, and the specification amended to indicate the SEQ ID NO.
- b) The amino acid sequence EXXYXQS and EXXYXQG disclosed on pages 9, line 26 have been added as SEQ ID NO: 22 and 23, respectively, and the specification amended to indicate these SEQ ID NOs.
- c) the amino acid sequence LEVLFQGP, disclosed on page 10, line 2 has been added as SEQ ID NO: 16, and the specification amended to indicate the SEQ ID NO.
- d) the amino acid sequence His-Glu-x-x-His, disclosed on page 20, line 23 has been added as SEQ ID NO: 17, and the specification amended to indicate the SEQ ID NO.
- e) the nucleotide sequence disclosed in Figure 1A has been added as SEQ ID NO: 18.
- f) The amino acid sequence from positions 1-22 disclosed in Figure 1B has been added as SEQ ID NO: 19.
- g) The amino acid sequence from position 497 to the carboxy terminus of the sequence disclosed in Figure 5 has been added as SEQ ID NO: 20.
- h) The nucleotide sequence disclosed in Figure 10 has been added as SEQ ID NO: 21 and the deduced amino acid sequence is added as SEQ ID NO: 24.
- i) Relevant paragraphs within the Brief Description of the Drawings have been amended to refer to the specified SEQ ID Nos.

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Applicants would make the following additional remarks.

- 1) Additional sequences disclosed on page 9 were not made part of the Sequence Listing since they contain less than 4 specifically identified amino acids, as defined in 37 CFR 1.821(a).
- 2) Additional amino acid sequences present on page 20 were not made part of the sequence listing since they are all embraced by new SEQ ID NO:17.
- 3) The amino acid sequence from positions 480 to 496 in Figure 1B and Figure 5 was not given a separate SEQ ID NO: since this sequence is already contained within SEQ ID NO: 15.

No new matter is added as a result of this amendment.

Finally, a request for formal drawings was enclosed with the Notice to Comply as part of Paper No. 7. However, Applicants already provided formal drawings with their correspondence of October 4, 2000, and therefore respectfully believe that this request was made in error. While no fee is thought due in connection with this amendment, if applicants are in error please use our Deposit Account 01-0885.

Respectfully submitted,

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A handwritten signature in black ink that appears to read "Carlos A. Fisher".



MARKED UP VERSION OF THE AMENDMENTS

Please replace the 2 paragraphs on page 13, lines 12-16 with the following:

– Figure 1A is a diagrammatic view of the single-chain TeTx construct in plasmid pTrcHisA and the nucleotide sequence of the junction region (SEQ ID NO: 18).

Figure 1B shows the amino acid sequence connecting the carboxyl terminus of the L chain and the amino terminus of the H chain and an engineered loop region containing an enterokinase cleavage site. The amino acid sequence of the upstream untranslated region is indicated as SEQ ID NO: 19.—

Please replace the paragraph on page 14, lines 8-11 with the following:

--Figure 5 is a depiction of the peptide fragments generated upon incubation of the recombinant single-chain TeTx with trypsin and Arg C protease, and deduction, from the N-terminal sequences of one of the resulting fragments (SEQ ID NO: 20) of the amino acid sequence recognized by these agents. --

Please replace the paragraph on page 14, lines 22-24 with the following:

--Figure 10 shows the scheme for construction of a plasmid encoding single-chain BoNT/E, and an agarose gel electrophoretogram of the PCR fragment (SEQ ID NO: 21) obtained during the construction of the plasmid, along with the deduced amino acid sequence of the fragment (SEQ ID NO: 24).—

Please replace the paragraph beginning on page 9, line 19 of the specification with the following paragraph.